A Randomized Multicenter Clinical Trial of Ultrathin Descemet Stripping Automated Endothelial Keratoplasty (DSAEK) versus DSAEK

Mor M. Dickman, MD,1 Pieter J. Kruit, MD, PhD,2 Lies Remeijer, MD, PhD,3 Jeroen van Rooij, MD,3 Allegonda Van der Lelij, MD, PhD,4 Robert H.J. Wijdh, MD,5 Frank J.H.M. van den Biggelaar, PhD,1 Tos T.J.M. Berendschot, PhD,1 Rudy M.M.A. Nuijts, MD, PhD1

Objective: To compare visual acuity, refraction, endothelial cell density (ECD), and complications after Descemet stripping automated endothelial keratoplasty (DSAEK) and ultrathin DSAEK (UT-DSAEK).

Design: A multicenter, prospective, double-masked, randomized, controlled clinical trial.

Participants: From 66 patients with irreversible corneal endothelial dysfunction due to Fuchs’ dystrophy who enrolled from 4 tertiary medical centers in the Netherlands, 66 eyes were studied.

Methods: Participants were centrally randomized to undergo either UT-DSAEK or DSAEK, based on preoperative best spectacle-corrected visual acuity (BSCVA), recipient central corneal thickness, patient age, and recruitment center. Donor corneas were precut by a single cornea bank.

Participants: Participants underwent ophthalmic examinations preoperatively and 3, 6, and 12 months after the operation, including manifest refraction, BSCVA using an Early Treatment Diabetic Retinopathy Study chart, and endothelium imaging.

Main Outcome Measures: BSCVA 12 months postoperatively.

Results: Preoperative BSCVA did not differ between patients undergoing DSAEK (0.35 logarithm of the minimum angle of resolution [logMAR] [95% confidence interval (CI) 0.27–0.43]; n = 32) and UT-DSAEK (0.37 logMAR [95% CI 0.31–0.43]; n = 34; P = 0.8). BSCVA was significantly better after UT-DSAEK compared with that after DSAEK at 3 months (0.17 logMAR [95% CI 0.13–0.21], n = 31 vs. 0.28 logMAR [95% CI 0.23–0.33], n = 31; P = 0.001), 6 months (0.14 logMAR [95% CI 0.10–0.18], n = 30 vs. 0.24 logMAR [95% CI 0.20–0.28], n = 30; P = 0.002), and 12 months (0.13 logMAR [95% CI 0.09–0.17], n = 33 vs. 0.20 logMAR [95% CI 0.15–0.25], n = 28; P = 0.03). Refraction, ECD loss (40% at 3 months; P < 0.001), donor loss (DSAEK n = 2 vs. UT-DSAEK n = 3 [relative risk (RR) 1.4 (95% CI 0.24–7.5); P = 0.7]), and graft dislocation (DSAEK n = 5 vs. UT-DSAEK n = 5 [RR 1.0 [95% CI 0.34–3.33]; P = 0.9]) did not differ between UT-DSAEK and DSAEK. Donor thickness was significantly thinner for UT-DSAEK (101 μm [95% CI 93–110 μm]; range 50–145 μm) than for DSAEK (209 μm [95% CI 196–222 μm]; range 147–289 μm; P < 0.001).

Conclusions: This study indicates that compared with DSAEK, UT-DSAEK results in faster and better recovery of BSCVA with similar refractive outcomes, endothelial cell loss, and incidence of complications. Ophthalmology 2016;123:2276-2284 © 2016 by the American Academy of Ophthalmology

Supplementary material is available at www.aaojournal.org.

Descemet stripping automated endothelial keratoplasty (DSAEK) is currently the predominant transplantation technique for patients with visually disabling corneal endothelial dysfunction, accounting for about half of all corneal transplantations performed in the United States.1

In DSAEK, the diseased corneal endothelium and Descemet membrane are selectively removed and donor corneal endothelium is transplanted on a carrier of Descemet membrane and posterior stroma of variable thickness harvested using a mechanical microkeratome. Compared with traditional penetrating keratoplasty (PK), DSAEK offers functional advantages such as decreased postoperative corneal astigmatism. However, visual acuity may be suboptimal following DSAEK.2

A much-debated question in the literature is the relationship between graft thickness and visual outcome. In 2011, Neff et al10 published the first evidence that thinner grafts could result in better vision. This publication was followed by additional studies that provided contradictory evidence.3-9

In 2013, Busin et al10 published the results of a prospective noncomparative case series that showed that ultrathin (UT) DSAEK grafts, intended to be thinner than 130 μm, result in better visual acuity compared with that of previously

2276 © 2016 by the American Academy of Ophthalmology
Published by Elsevier Inc.
reported grafts. However, studies supporting and rejecting a relationship between graft thickness and visual acuity are limited by retrospective design, heterogeneity in graft thickness measurement techniques, and nonstandardized visual acuity measurements. To the best of our knowledge, no randomized, controlled clinical trial (RCT) has been performed to compare DSAEK with UT-DSAEK. The UT-DSAEK study, a multicenter, prospective, double-masked RCT, was designed to compare visual and refractive outcomes, endothelial cell (EC) loss, and incidence of complications after DSAEK and UT-DSAEK.

Methods

This RCT (UT-DSAEK Study) was conducted in 4 tertiary medical centers in the Netherlands. The institutional review boards of all participating centers approved the study. Informed consent was obtained from all participants, who were recruited between June 2013 and April 2014. Since October 2011, the trial has been registered in the Dutch trial register as the Ultrathin DSAEK study (identifier NTR 3104; available at: www.trialregister.nl, accessed June 21, 2016). The trial was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were adult patients with irreversible corneal endothelial dysfunction due to Fuchs’ dystrophy who required corneal transplantation and who had no coexisting vision-limiting comorbidities other than cataract. Exclusion criteria were previous corneal transplantation in the study eye, human leukocyte antigen—typed corneal transplantation, or an inability to follow instructions or complete follow-up.

Each participant’s medical history was recorded, and all eligible patients underwent a comprehensive ophthalmic examination including slit-lamp examination, manifest refraction, best spectacle-corrected visual acuity (BSCVA) using an Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart (Vector Vision, Greenville, OH), and posterior segment spectral-domain ocular coherence tomography (Spectra; Heidelberg Engineering GmbH, Heidelberg, Germany).

Donor Preparation

Donor corneas were precut by a single cornea bank (Euro Tissue Bank, Beverwijk, the Netherlands). Donor tissue was preserved according to conventional eye-bank techniques. The selection criteria of the donor cornea for DSAEK or UT-DSAEK were the same. After a short hypothermic storage between recovery and arrival at the bank, corneoscleral buttons were dissected and stored in organ culture comprising minimum essential medium (Biowest, Nuaillé, France) supplemented with 25 mmol/l 4-(2-hydroxyethyl)-1-piperazinethanesulfonic acid, 26 mmol/l sodium bicarbonate, 5.5 mmol/l glucose, 2 mmol/l L-glutamine, 1 mmol/l pyruvate, 2% (vol/vol) newborn calf serum, 10 IU/ml penicillin, 0.1 mg/ml streptomycin, and 0.25 μg/ml amphotericin at 31°C. To allow deturgescence, corneoscleral buttons were transferred to a transport medium supplemented with 6% dextran (Sigma Aldrich, St. Louis, MO) before and immediately after dissection. Graft dissection was performed with the Gebauer SLc microkeratome system (Gebauer Medizintechnik GmbH, Neuhausen, Germany) using a single-pass technique, aiming at a central residual stromal bed thickness of 200±20 μm for DSAEK and 100±20 μm for UT-DSAEK. Donor and lamellar corneal thickness were measured at the cornea bank using anterior-segment optical coherence tomography (AS-OCT; Cassia SS-1000; Tomey, Nagoya, Japan).

Surgical Procedure

Surgical procedures were performed by 5 experienced corneal surgeons (L.R., J.v.R., A.V.d.L., R.H.J.W., and R.M.M.A.N.), who had each performed >200 DSAEK operations prior to the study. DSAEK and UT-DSAEK were similarly performed according to a standardized operative technique. Patients were either pseudophakic prior to corneal transplantation or underwent a triple procedure consisting of phacoemulsification and intraocular lens implantation followed by corneal transplantation. No staged procedures were performed. The triple procedure was performed in 10 patients in the DSAEK group and 10 patients in the UT-DSAEK group. In this procedure, a 4.5-mm incision was made in the recipient eye, and the Descemet membrane and endothelium of the recipient were scored using a reversed Pri-cé—Sinskey hook (Moria, Antony, France) under a viscoelastic substance (Healon; Abbott Medical, Uppsala, Sweden).

A precut donor graft was trephined and the diameter was based on the corneal diameter of the recipient. The donor graft was then inserted using either a Busin glide (Moria; n = 33) or a Tan Endoglide (Angiotech Pharmaceuticals, Reading, PA; n = 33) followed by the insertion of air into the anterior chamber to unfold the donor graft and approximate it against the recipient stroma. Complete air fill was maintained for 10 minutes, and the procedure was completed with partial replacement of air with balanced salt solution (Alcon Ltd, Fort Worth, TX), leaving an air bubble of approximately 6 mm in place to further stabilize the donor graft. An occlusive patch was applied, and patients remained in the supine position during the first 24 hours postoperatively. Rebubbleling, involving the injection of an anterior-chamber air bubble and graft refloafting, was performed in cases of large, central, or complete graft detachment. Partial or focal detachments beyond the visual axis were observed, awaiting spontaneous reattachment. Postoperatively, all patients received the same topical treatment schedule. Topical dexamethasone 0.1% drops (Ratiopharm, Zaandam, the Netherlands) were tapered as follows: 6 times daily for 3 months, 4 times daily for 1 month, 3 times daily for 1 month, 2 times daily for 1 month, and 1 time daily thereafter. Topical chloramphenicol 0.5% drops (Ratiopharm) were given 3 times daily for the first 3 months only.

Outcome Measures

The main outcome measure of our study was high-contrast BSCVA 12 months postoperatively. Secondary outcome measures included refraction, EC density (ECD), and complication profile. Manifest refraction and BSCVA were recorded at each center by a single masked, certified optometrist preceding any examination requiring administration of eye drops or contact with the eye. Auto refraction was taken as the starting point for manifest refraction and was determined using a phoropter and a cross cylinder technique for cylinder refraction. Lighting conditions were controlled with ambient light set to mesopic levels (3 lux). The ETDRS score was recorded using the ETDRS letter chart at 4 meters and converted to logarithm of the minimum angle of resolution (logMAR) as follows: the log score of the last row where the patient correctly identified all 5 letters was identified (e.g., 0.10 log row) and 0.02 log units were then subtracted for every letter that was correctly identified beyond the last row (e.g., 0.10 log row + 3 letters on the 0.00 log row = 0.10 — (2 × 0.02) = 0.06 logMAR). Eyes reading <20 letters correctly at 4 meters were tested at 1 meter adding a +0.75 diopter (D) sphere correction. Refractive shift was determined by the difference of mean spherical equivalent between follow-up and preoperative values. In patients undergoing a triple procedure, refractive shift was determined by subtracting the biometric target refraction (~1 D) from achieved refraction. Preoperatively, the donor ECD was determined at the
eye bank by means of manual cell counting using a light microscope after trypan blue vital staining to improve mosaic visualization. Postoperatively, 3 images of the central endothelium were captured at each visit using either specular microscopy (Topcon, Nagoya, Japan) or confocal microscopy (Nidek, Aichi, Japan). The ECD was determined using the standard corner method. To reduce sampling error, images were analyzed by a single certified, masked technician at each site, who manually defined the borders of 50 ECs in the center of each image. The final ECD at each visit was the average of 3 central counts.

All outcome parameters were recorded preoperatively and 3, 6, and 12 months postoperatively. Posterior segment spectral-domain optical coherence tomography was performed preoperatively and during the first postoperative study visit to detect cystoid macular edema (CME) as an adverse event. CME was defined as any increase in central macular thickness >30% compared with the baseline value, irrespective of the presence or absence of cystoid abnormalities on ocular cohesive tomography results.

Sample Size
Sample size was calculated based on previous studies that indicated an expected mean of 0.1 logMAR BSCVA in the study group and a difference in BSCVA of 0.15 logMAR between DSAEK and UT-DSAEK, with a standard deviation of 0.2 logMAR. Assuming 2 of 0.05 (2-sided) and a power of 80%, this yielded a sample size of 58 patients. Accounting for an anticipated dropout rate of 15%, 69 patients were required. However, the actual dropout rate was lower than expected (6%), which means 62 were available for analysis.

Randomization and Blinding
Minimization randomization was performed centrally by an independent investigator from the Clinical Trial Center Maastricht (www.ctcm.nl) using a web-based random sequence generator (Trans European Network for Clinical Trials Services, TENALEA, available at www.tenalea.net, accessed June 21, 2016) based on preoperative ETDRS BSCVA, recipient central corneal thickness, patient age, and recruitment center. Allocation assignment was then sent only to the cornea bank (Euro Tissue Bank), which precut the donor corneas. The actual dropout rate was 6%. In the UT-DSAEK group, 1 patient died shortly after the 3-month follow-up visit and 2 patients were lost to follow-up at the last study visit.

Baseline Patient and Donor Characteristics
Baseline patient and donor characteristics are given in Table 1. Visual and refractive outcomes and ECD are given in Table 2. Grafts were significantly thinner for UT-DSAEK (101 μm [95% confidence interval [CI] 93−110 μm]; range 50−145 μm) compared with that of DSAEK (209 μm [95% CI 196−222 μm]; range 147−289 μm; P < 0.001). Graft thickness was the only donor or recipient parameter that differed significantly between both groups preoperatively (Table 1).

Visual Outcomes
Visual outcomes are shown in Figure 2. Postoperatively, BSCVA was significantly better in the UT-DSAEK group compared with that of DSAEK (209 μm [95% CI 196−222 μm]; range 147−289 μm; P < 0.001), which indicates a strong relationship. Linear mixed-model sensitivity analysis showed a significant postoperative difference in BSCVA in favor of UT-DSAEK at 3 months (−0.12 logMAR; P < 0.001 [95% CI −0.17 to −0.07]); 6 months (−0.09 logMAR; P = 0.001 [95% CI −0.15 to −0.041]); and 12 months (−0.07 logMAR; P = 0.021 [95% CI −0.12 to −0.01]). Postoperative AS-OCT central graft thickness measurements were available for 42 patients. Complete case analysis, including only cases with complete data, showed a significant relationship both between preoperative central graft thickness and BSCVA at 12 months (r = 0.49; N = 42; P = 0.01) and between postoperative central graft thickness and BSCVA at 12 months (r = 0.59; N = 42, P < 0.001) (Supplementary Figs S1A and S1B, available at www.aaojournal.org). The correlation coefficient between preoperative and postoperative central graft thickness was r = 0.9 (N = 42; P < 0.001), which indicates a strong relationship. Figure 3 shows representative images of eyes after UT-DSAEK and DSAEK (Fig 3A) and corresponding AS-OCT images taken 1 year after surgery (Fig 3B) and immediately after graft dissection (Fig 3C).

Refractive Outcomes and Endothelial Cell Density
Spherical equivalent did not differ between the DSAEK and UT-DSAEK groups preoperatively and postoperatively. Likewise, a comparable postoperative hyperopic shift was noted in both groups (Table 2).
The ECD did not differ between the DSAEK and UT-DSAEK groups (Table 2). Compared with the donor cell density, the ECD decreased significantly in both groups 3 months after surgery, by 40% ($P < 0.001$), and stabilized thereafter. Neither the type of glide used to insert the donor nor combined cataract surgery (triple procedure) was significantly related with ECD in our study, and these factors were therefore not included in the final model for ECD analysis.

Figure 1. Participant flow diagram.

Table 1. Baseline Patient and Donor Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DSAEK ($n = 32$), Mean ± SD (95% CI)</th>
<th>UT-DSAEK ($n = 34$), Mean ± SD (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>$71±10$ (67–75)</td>
<td>$73±18$ (67–79)</td>
<td>0.6</td>
</tr>
<tr>
<td>ETDRS BSCVA (logMAR)</td>
<td>$0.35±0.22$ (0.27–0.43)</td>
<td>$0.37±0.18$ (0.31–0.43)</td>
<td>0.8</td>
</tr>
<tr>
<td>Central corneal thickness ($\mu$m)</td>
<td>$641±64$ (618–664)</td>
<td>$643±62$ (621–665)</td>
<td>0.9</td>
</tr>
<tr>
<td>Spherical equivalent (diopter)</td>
<td>$−0.80±1.0$ (−1.16 to −0.04)</td>
<td>$−0.5±0.9$ (−0.83 to −0.17)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Baseline donor characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>$69±11$ (65–72)</td>
<td>$68±9$ (65–71)</td>
<td>0.7</td>
</tr>
<tr>
<td>Death to enucleation (hrs)</td>
<td>$13±6$ (11–15)</td>
<td>$13±7$ (11–15)</td>
<td>0.6</td>
</tr>
<tr>
<td>Death to preservation (hrs)</td>
<td>$24±11$ (20–28)</td>
<td>$23±11$ (19–27)</td>
<td>0.9</td>
</tr>
<tr>
<td>Organ culture preservation (days)</td>
<td>$12±5$ (10–14)</td>
<td>$12±4$ (11–13)</td>
<td>0.7</td>
</tr>
<tr>
<td>Transport medium (days)</td>
<td>$3±0.6$ (2.8–3.2)</td>
<td>$3±0.8$ (2.7–3.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>ECD (cells/mm²)</td>
<td>$2675±158$ (2617–2732)</td>
<td>$2639±97$ (2605–2673)</td>
<td>0.3</td>
</tr>
<tr>
<td>Central graft thickness ($\mu$m)</td>
<td>$209±37$ (196–222)</td>
<td>$101±24$ (93–110)</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

BSCVA = best spectacle-corrected visual acuity; CI = confidence interval; DSAEK = Descemet stripping automated endothelial keratoplasty; ECD = endothelial cell density; ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; UT-DSAEK = ultrathin Descemet stripping automated endothelial keratoplasty.
Intraoperative and Postoperative Complications

Donor tissue loss (relative risk, 1.4 [95% CI 0.24–7.5]; P = 0.7) and graft dislocation (relative risk, 1.0 [95% CI 0.34–3.33]; P = 0.9) did not differ between the 2 study groups (Table 2). CME and rejection episodes were not noted in either group during the study follow-up period.

Discussion

The results of this multicenter RCT provide a comparison of visual and refractive outcomes, EC losses, and complication profiles between DSAEK and UT-DSAEK during a follow-up period of 1 year. Compared with DSAEK results, we found faster recovery and better visual acuity with a comparable hyperopic shift, EC loss, and incidence of complications after UT-DSAEK.

The introduction of endothelial keratoplasty (EK) has revolutionized corneal transplantation during the past decade. In the United States and in Europe, DSAEK replaced PK as the most common type of corneal transplantation, while Fuchs’ endothelial dystrophy has become the most common indication for corneal transplantation. The main advantages of DSAEK over PK are faster visual

---

Table 2. Outcomes after Descemet Stripping Automated Endothelial Keratoplasty and Ultrathin Descemet Stripping Automated Endothelial Keratoplasty

<table>
<thead>
<tr>
<th></th>
<th>DSAEK, Mean ± SD [95% CI] (n or %)</th>
<th>UT-DSAEK, Mean ± SD [95% CI] (n or %)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETDRS BSCVA (logMAR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mos after surgery</td>
<td>0.28±0.14 [0.23–0.33] (31)</td>
<td>0.17±0.11 [0.13–0.21] (31)</td>
<td>0.001*</td>
</tr>
<tr>
<td>6 mos after surgery</td>
<td>0.24±0.11 [0.20–0.28] (30)</td>
<td>0.14±0.11 [0.10–0.18] (30)</td>
<td>0.002*</td>
</tr>
<tr>
<td>12 mos after surgery</td>
<td>0.20±0.12 [0.15–0.25] (29)</td>
<td>0.13±0.12 [0.09–0.17] (33)</td>
<td>0.030*</td>
</tr>
<tr>
<td>Spherical equivalent (D)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mos after surgery</td>
<td>−0.03±1.2 [−0.46 to 0.40] (32)</td>
<td>0.13±1.1 [−0.26 to 0.52] (33)</td>
<td>0.24</td>
</tr>
<tr>
<td>6 mos after surgery</td>
<td>−0.12±1.1 [−0.57 to 0.37] (32)</td>
<td>0.14±0.97 [−0.21 to 0.49] (32)</td>
<td>0.35</td>
</tr>
<tr>
<td>12 mos after surgery</td>
<td>−0.17±1.3 [−0.66 to 0.32] (29)</td>
<td>0.23±0.97 [−0.11 to 0.57] (33)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hyperopic shift (D)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mos after surgery</td>
<td>0.86±1.10 [0.45–1.27] (30)</td>
<td>0.74±1.22 [0.28–1.20] (30)</td>
<td>0.70</td>
</tr>
<tr>
<td>6 mos after surgery</td>
<td>0.78±1.31 [0.31–1.25] (32)</td>
<td>0.65±0.98 [0.30–1.00] (32)</td>
<td>0.67</td>
</tr>
<tr>
<td>12 mos after surgery</td>
<td>0.60±1.33 [0.10–1.10] (29)</td>
<td>0.71±1.00 [0.34–1.08] (33)</td>
<td>0.72</td>
</tr>
<tr>
<td>ECD (cells/mm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mos after surgery</td>
<td>1787±301 [1668–1906] (27)</td>
<td>1623±378 [1482–1764] (30)</td>
<td>0.08</td>
</tr>
<tr>
<td>6 mos after surgery</td>
<td>1778±386 [1628–1928] (28)</td>
<td>1594±405 [1440–1748] (29)</td>
<td>0.09</td>
</tr>
<tr>
<td>12 mos after surgery</td>
<td>1635±378 [1485–1785] (27)</td>
<td>1533±399 [1384–1682] (30)</td>
<td>0.33</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor perforation</td>
<td>2 (6%)</td>
<td>3 (9%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Graft dislocation</td>
<td>5 (16%)</td>
<td>5 (15%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Primary graft failure</td>
<td>(−)</td>
<td>1 (3%)</td>
<td>(−)</td>
</tr>
</tbody>
</table>

BSCVA = best spectacle-corrected visual acuity; CI = confidence interval; D = diopter; DSAEK = Descemet stripping automated endothelial keratoplasty; ECD = endothelial cell density; ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; UT-DSAEK = ultrathin Descemet stripping automated endothelial keratoplasty.

*Corrected P values according to Benjamini and Hochberg refer to BSCVA at 3, 6, and 12 months, respectively: P ≤ 0.02 at 3 months (0.001), P ≤ 0.03 at 6 months (0.002), P ≤ 0.05 at 12 months (0.030), were considered significant, respectively.

---

Figure 2. Best spectacle-corrected visual acuity (BSCVA) in both treatment groups. DSAEK = Descemet stripping automated endothelial keratoplasty; logMAR = logarithm of the minimum angle of resolution; UT-DSAEK = ultrathin Descemet stripping automated endothelial keratoplasty.
rehabilitation, less severe astigmatism, avoidance of ocular surface disease, and fewer graft rejections. However, best-corrected visual acuity after DSAEK may be suboptimal, which has led to interest in novel EK techniques. Although UT-DSAEK has been suggested to achieve better vision, this hypothesis remains controversial.

This RCT was designed to compare visual and refractive outcomes, EC loss, and incidence of complications after DSAEK and UT-DSAEK. Minimization randomization was chosen to ensure treatment arms were balanced with respect to predetermined prognostic factors and the number of patients in each group. The number of participants was balanced, and graft thickness was the only donor or recipient parameter that differed significantly between groups (Table 1), indicating that randomization was successful.

The main outcome measure of our study was high-contrast BSCVA. We found faster and better visual recovery following UT-DSAEK compared with that following DSAEK 3, 6, and 12 months postoperatively. Visual acuity after DSAEK in our study compared favorably with that previously reported in the literature. This finding may be attributed to careful selection of patients without vision-limiting comorbidity, standardization of surgical technique over the past decade, or the experience of the surgical team. However, whereas visual acuity after UT-DSAEK in our study was considerably better than that reported in the literature for DSAEK, it was lower than values reported by Busin et al after UT-DSAEK.

Previous reports have suggested several factors that may limit best-corrected vision following DSAEK, including a donor-recipient stromal interface and curvature mismatch, tissue irregularities, posterior corneal higher-order aberrations, and anterior corneal scarring. Thinner grafts have been shown to result in a more regular posterior corneal surface and to induce fewer higher-order aberrations, which may explain the faster and better visual recovery following UT-DSAEK. We found a moderate relationship between preoperative central graft thickness and BSCVA at 12 months and a strong relationship between 12-month postoperative central graft thickness and BSCVA. (Supplementary Fig S1A and B, available at www.aaojournal.org). Importantly, correlation coefficients do not imply causality, and whereas UT-DSAEK resulted in significantly better visual acuity, the observed effect size does not allow accurate prediction of visual outcome based on graft thickness on an individual basis.
Recent studies report gradual improvement in visual acuity up to 5 years after DSAEK, suggesting ongoing corneal remodeling after restoration of endothelial function.\textsuperscript{3,28} Long-term follow-up is needed to determine the difference in improvement of visual acuity after DSAEK and UT-DSAEK, which may affect the results of this RCT if it were to be extended. We recognize that the clinical impact of the difference in visual acuity of 0.07 logMAR (nearly 1 Snellen line) between DSAEK and UT-DSAEK at 12 months in our study may be limited.

Our primary outcome measure, high-contrast visual acuity, represents the small-angle domain of the retinal point-spread function and therefore does not cover all aspects of quality of vision.\textsuperscript{25} Although final visual acuity after DSAEK is often suboptimal, we previously showed that most patients report subjective improvement in vision and vision-related quality of life,\textsuperscript{26} probably because of improvement in other domains of vision. Indeed, van der Meulen et al\textsuperscript{31} reported improvement in stray light (disability glare) after EK, an objective measure of the large-angle domain of the retinal point-spread function.

DSAEK is known to result in a postoperative hyperopic shift of 0.7 to 1.5 D, with an average induced hyperopia of 1.1 D,\textsuperscript{2} that has been attributed to the meniscus shape profile of the donor lenticule.\textsuperscript{27,28} In our study, a comparable hyperopic shift of 0.8 D was observed after DSAEK and UT-DSAEK, indicating that central graft thickness does not influence refractive outcome. A hyperopic shift was also recently described after Descemet membrane endothelial keratoplasty in which anatomical restoration of the cornea is achieved, suggesting curvature changes due to corneal deturgescence are involved.\textsuperscript{29} Regardless of the underlying cause, a hyperopic shift should be taken into consideration when planning a triple or sequential procedure involving UT-DSAEK.

Early EC loss attributed to surgical trauma remains the Achilles’ heel of EK.\textsuperscript{30,31} In our study, EC loss was comparable following DSAEK and UT-DSAEK, measuring 40% in both groups 3 months after surgery. This finding suggests that neither a single-pass dissection nor periperative handling of UT grafts is associated with increased EC loss compared with that of DSAEK. The stabilization of EC counts in both arms of our study after 3 months is in line with recent reports suggesting that long-term EC loss after EK is comparable to PK, despite more early cell loss.\textsuperscript{32} Nevertheless, long-term follow-up is needed to determine the effect of early EC loss on UT-DSAEK graft survival.

With respect to complications, donor loss during graft dissection in our study was high and comparable between DSAEK and UT-DSAEK (Table 2). Whereas in the United States 74% of donors for DSAEK are precut by the cornea bank,\textsuperscript{33} in Europe the use of precut tissue has only recently gained popularity. For this study, a precut service was developed in the Netherlands. The high donor loss observed was likely due to the learning curve of eye-bank technicians. Graft dislocation, the most common complication after EK, occurred in 15% of cases in our study and did not differ between DSAEK and UT-DSAEK, suggesting that the presence of a stromal bed determines graft adhesion regardless of graft thickness within the graft thickness range of our study. In the UT-DSAEK group, 1 episode of primary graft failure occurred, requiring retransplantation. Examination of the surgical report suggests this unfortunate outcome was likely due to perioperative graft trauma. Postoperatively, CME was observed in neither group. This finding may be due to the timing of the first postoperative visit at 3 months, the self-limiting nature of CME, or the sample size of our study. Likewise, no graft rejection episode was noted in either group over a follow-up period of 1 year.

The EC loss and rebubbling rate in our study were higher than those reported in recent large case series from tertiary centers.\textsuperscript{34} Possible reasons for the enhanced dislocation rate and early EC loss include the time interval between cutting the lamella and surgery (3 days on average) and the effect of organ culture medium remnants on the graft, which may interfere with graft adherence. In addition, small technical differences in surgical protocol in a multicenter trial design or a lack of a central reading center may have influenced EC analysis. This study compared the outcomes of endothelial grafts at both ends of the thickness spectrum. Whereas graft thickness in the DSAEK group is thicker than the tissue that most DSAEK surgeons currently use, target thickness was based on clinical practice and our own experience at that time.\textsuperscript{3} It is important to bear in mind that organ culture, commonly used in Europe, results in significant corneal swelling and thicker grafts compared with cold storage, which is used in the United States. In the absence of consensus on the definition of UT grafts, the choice of graft thickness for the UT-DSAEK group was based on the literature that was available when the study was designed and that reported better visual outcomes with grafts thinner than 131 \(\mu m\) and aimed to an ideal thickness less than 100 \(\mu m\).\textsuperscript{35}

Also, in this study, we included only patients with Fuchs’ endothelial dystrophy without vision-limiting comorbidity treated in tertiary medical centers willing to complete the requested 12-month follow-up. Moreover, all surgeons were certified corneal specialists with extensive experience in lamellar corneal surgery. Whereas this reflects well the situation in the Netherlands, where guidelines of the Dutch Cornea Workgroup of the Netherlands Ophthalmological Society determine the qualifications required to perform corneal transplantation, it may not reflect the situation in other parts of the world. This is important in light of the Australian Corneal Graft Registry, which recently suggested worse vision and graft survival with EK compared with those of PK, and the UK National Transplant Registry, which showed that EK graft survival rates are higher when the surgical procedures are performed in experienced units.\textsuperscript{36,37}

In summary, the results of this multicenter RCT indicate that compared with DSAEK, UT-DSAEK leads to faster and better recovery of visual acuity with a similar hyperopic shift, EC loss, and incidence of complications within the assessed range of graft thicknesses. However, the observed effect size does not allow accurate prediction of visual outcome based on graft thickness on an individual basis, and long-term follow-up is needed to determine whether the
small difference in visual acuity between the groups at 1 year will be maintained.

Acknowledgments. The authors thank Friso W. van Marion, MD and the eye bank technicians of the Euro Tissue Bank for their support and assistance with this project. Special thanks also go to Janneke Bus, BSc, Sietse Huiskens, BSc, Caroline Jordaan, BSc, Nienke Soeters, PhD, Mark Willems, BSc, Arno Skrabanja, PhD, Yanny Y. Cheng, MD, PhD, Martin Millenaar, MD, and Jurriaan Brekelmans, MD, for their valuable contribution and dedication. Finally, the authors thank the Dutch Cornea Patient Organization (Hoonvliezen Patiënten Vereniging) for their support during all stages of the study.

References


Footnotes and Financial Disclosures

Originally received: April 10, 2016.
Final revision: July 23, 2016.
Accepted: July 25, 2016.

1 University Eye Clinic, Maastricht University Medical Center, the Netherlands.
2 Euro Tissue Bank, Beverwijk, the Netherlands.
3 Rotterdam Eye Hospital, the Netherlands.
4 Department of Ophthalmology, University Medical Center Utrecht, the Netherlands.
5 Department of Ophthalmology, University Medical Center Groningen, the Netherlands.


Financial Disclosure(s):
The author(s) have made the following disclosure(s): M.M.D., F.J.H.M.v.d.B., T.T.J.M.B., R.M.M.A.N.: Grants — ZonMw, the Nederlands Association for Health Research and Development; Stichting Nederlands Oogheelkundig Onderzoek; Dr F.P. Fischer-Stichtin; Landelijke Stichting Blinden en Slechtzienden; Rotterdamse Stichting Blindenbelangen.

Supported by grants from ZonMw, The Hague, the Netherlands Association for Health Research and Development; Stichting Nederlands Oogheelkundig Onderzoek (SNOO), Nijmegen, The Netherlands; Dr. F.P. Fischer-Stichting, Utrecht, The Netherlands; Landelijke Stichting Blinden en Slechtzienden (LSBS), Ede, The Netherlands; and the Rotterdamse Stichting Blindenbelangen (RSB), Rotterdam, The Netherlands. None of the authors has any proprietary/financial interests to disclose with regard to this study.

Author Contributions:
Conception and design: Dickman, Remeijer, van Rooij, Van der Lelij, Wijdh, van den Biggelaar, Berendschot, Nuijts
Analysis and interpretation: Dickman, van den Biggelaar, Berendschot, Nuijts
Data collection: Dickman, Kruit, Remeijer, van Rooij, Van der Lelij, Wijdh, van den Biggelaar, Nuijts
Obtained funding: none
Overall responsibility: Dickman, Kruit, Remeijer, van Rooij, Van der Lelij, Wijdh, van den Biggelaar, Berendschot, Nuijts

Abbreviations and Acronyms:
AS-OCT = anterior segment optical coherence tomography; BSCVA = best spectacle-corrected visual acuity; CI = confidence interval; CME = cystoid macular edema; D = diopter; DSAEK = Descemet stripping automated endothelial keratoplasty; EC = endothelial cell; ECD = endothelial cell density; EK = endothelial keratoplasty; ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = logarithm of the minimum angle of resolution; PK = penetrating keratoplasty; RCT = randomized, controlled clinical trial; UT = ultrathin.

Correspondence:
Mor M. Dickman, MD, University Eye Clinic, Maastricht University Medical Center, Postbus, 6202 AZ Maastricht, the Netherlands. E-mail: mor.dickman@mumc.nl.